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A DISSERTATION SUBMITTED TO THE FACULTY OF THE DIVISION OF THE BIOLOGICAL SCIENCES IN CANDIDACY FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

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STUDIES ON THE ACTION OF THE ALKALI IODIDES

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The demonstration of the importance of the element iodine for the normal function of the thyroid gland and its subsequent extensive use in the prevention of goitre has stimulated a number of investigations on the action of this element and its alkali salts on the mammalian organism.

Macela (1925) reported that the addition of 0.2 mgm. NaI daily to the diet of rats produced a greater increase in weight and more rapid sexual development than was observed in control animals. This was confirmed by Hanzlik, Talbot and Gibson (1928) and Kochman (1931) who concluded that it was due to a lowering of the basal metabolism. Mendel and Vickery (1930) reported that the daily administration of 1.1 mgm. KI to the diet of rats for 200 to 400 days had no effect on the weight of growing rats. Evvards and Culbertson (1925) reported that growing pigs receiving 0.01 per cent KI daily showed an average weight increase 10 per cent greater than the control animals.

Grey and Loeb (1928) reported that small amounts of I caused stimulation of the thyroid gland of the guinea pig during the first three or four weeks of administration, but after this time I caused depression of thyroid function. Rabinowitch (1930) using the number of mitotic figures as an index of activity, confirmed this finding in the guinea pig. Chouke (1930) found that small amounts of KI administered for periods of 10 to 30 days had no noticeable effect on the thyroid of the rat. Webster and Chesney (1928) reported that although Lugol's solution caused a slight reduction in the basal metabolic rate of rabbits, it produced no changes in the thyroid.

Cases of thyrotoxicosis in supposedly normal individuals as the result of excess iodine intake have been reported by Buchholz (1918), Scheick (1930), Herzfeld (1931), Holm (1931), Raab (1931) and Zimmermann (1931). All these reports are subject to the criticism that the functional condition of the thyroid previous to the iodine administration was not known.

The action of iodides on the gonads was reported by Jastram (1920) who states that alkali iodides in doses under 2.0 grams per day caused an

[1] Aided by a grant from the Henry Strong Denison Foundation.

increased connective tissue formation in the ovaries of puppies; and by Buchhelm (1932) who reported that small amounts of iodine cause arrested development of the seminal vesicles of mice, rats and guinea pigs, but no interference with normal spermatogenesis.

Massimo (1930) reports that rabbits given 100 to 200 mgm. of KI per kgm. for 7 to 25 days show hemorrhagic infiltrations between the myocardial fibers and round cell infiltrations beneath the endocardium.

Sgalitzer (1908) reported the acute effects of large doses of NaI. Subcutaneous administration of 1.2 gram of NaI per kgm. to rabbits caused death in a few days. At autopsy there was marked fatty degeneration of the liver, frequent pleural effusion and pulmonary edema. Smaller doses caused severe diarrhea, loss of weight, and inanition. A characteristic effect produced was a decrease in voluntary movements of the animal, paralysis of the hind limbs, and marked dyspnea. Prolonged administration of smaller amounts produced a tolerance to the drug. Wadi (1928), also using rabbits, reported that 0.5 gram KI per kgm. orally per day produced a gradual loss of weight. He also reports the development of tolerance to the drug. At autopsy there was no pleural effusion, but marked hyperemia and edema of the lungs. The testicles were normal; the thyroid showed marked flattening of the acinar epithelium, and both normal and KI fed animals showed frequent fatty degeneration of the liver. Shoemaker and Underhill (1932) also state that administration of 0.5 gram KI per kgm. orally caused death in 2 to 4 days. Chiari and Januschke (1910) reported that the intravenous injection of NaI in dogs caused marked pleural effusions, which was confirmed by Chu and How (1931) but denied by Gold (1928) who used twice the dose of iodide used by Chiari and Januschke.

These discrepancies in the literature as to the effect of the alkali iodides suggested further studies on their effects in the rabbit.

Methods and materials. Experiments on the effect of iodides on growth were carried out on litter-mate animals raised in this laboratory. The thyroids were examined at biopsy, and a section removed for histological examination 1 or 2 weeks before administration of KI. KI was given orally in small capsules or subcutaneously in isosmotic solution (2.55 per cent KI). Weight, appetite, and consistency of the feces were recorded daily. At the conclusion of the experiment the animals were killed by a blow on the head and autopsy was carried out at once. The thyroid and sections of the heart, lungs, kidneys, adrenals, liver and ovaries or testes were fixed in Zenker's or Bouin's fluid and stained with hematoxylin and eosin. The results of these experiments carried out on three litters are shown in figures 1 to 3.

The effect of KI given subcutaneously in large doses on adult animals was studied on 5 animals weighing between 2000–2200 grams. Five

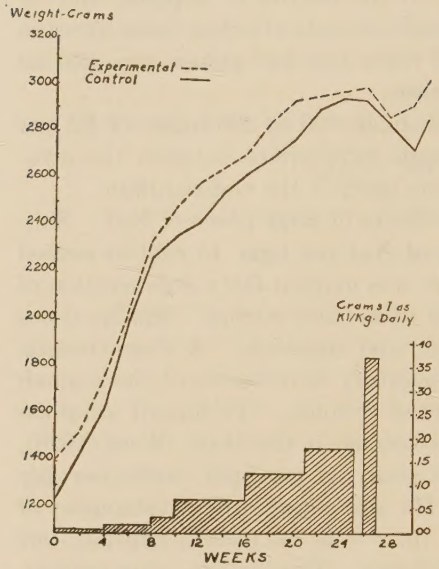

Fig. 1. Experimental, 2-control, 2 animals

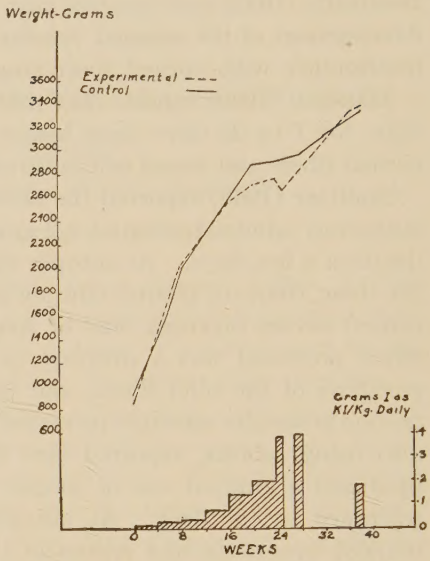

Fig. 2. Experimental, 4-control, 2 animals

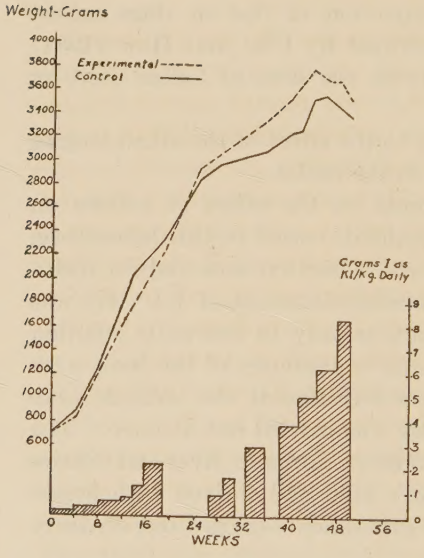

Fig. 3. Experimental, 5-control, 3 animals

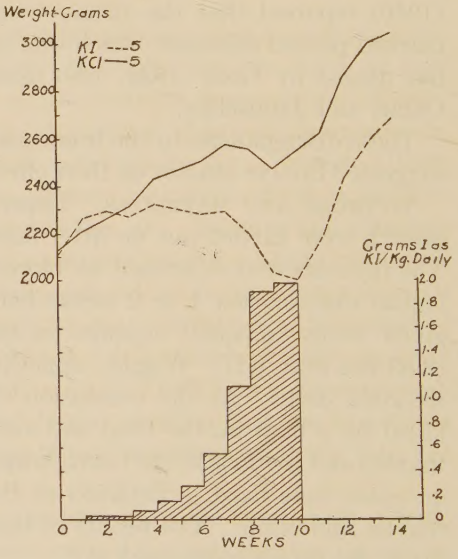

Fig. 4

control animals received an equivalent dose of KCl. The results are shown in figure 4.

The comparative effect of large doses of KI and NaI on young rabbits was studied on one litter, five animals receiving NaI and four KI subcutaneously. These results are shown in figure 5.

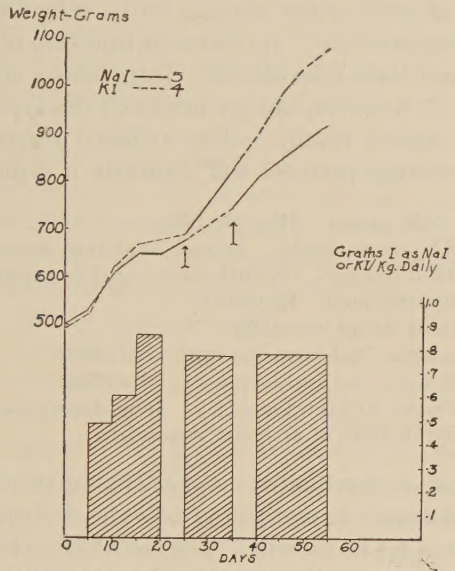

Fig. 5. NaI and KI interchanged between the period indicated by arrows

Results and discussion. *1. Growth.* The growth curves of the animals given KI orally (figs. 1 and 2) are not significantly different from those fed only on the stock diet. Diarrhea occurred occasionally in both experimental and control animals, with about equal frequency in both groups. The animals fed KI showed a polyuria and increased water intake, but in all other respects appeared to be normal. At autopsy there were no macroscopic changes in any organ except the thyroid, which was very hard and avascular. Pleural effusion or macroscopic evidence of fatty degeneration of the liver was never found in these animals.

Because of the difficulty experienced in giving KI quantitatively by mouth, another litter was given KI subcutaneously (2.55 per cent KI-fig. 3.). This concentration caused no cutaneous lesions even after months of injection. To rule out the potassium ion as the cause of any observed effects, the control animals received an equal volume of isomolar KCl. Both the experimental and control animals showed a marked polyuria and occasional diarrhea. When the dose of KI exceeded 0.5 gram per kgm. body weight, the characteristic flaccidity and paralysis of the hind limbs

observed by Sgalitzer appeared immediately following injection, but passed off within 20 to 30 minutes. This effect never appeared in the animals injected with KCl, and is definitely an action of the iodide ion. Two animals, after having received KI for 2 and 8 months respectively, went into severe convulsions, showed marked dyspnea, and died within 2 to 3 minutes following an injection of KI. This was most probably due to an accidental injection of some of the solution into a subcutaneous vein and is an effect of the potassium ion. Intravenous injection of NaI in twenty rabbits never produced these convulsions. Intravenous injection of small amounts of KI or KCl, however, always produced the typical convulsions and dyspnea which ended fatally unless artificial respiration was administered. The following protocol will illustrate a typical experiment.

Rabbit w 12. Male, 3150 grams. May 14, 1933.

2:00 p.m. 255 mgm. KI intravenously. Animal went into severe convulsions at once; marked dyspnea, exophthalmos, cardiac arrest. Artificial respiration administered. Recovery.
2:06 p.m. Animal walking about normally.
2:10 p.m. Injected 232 mgm. NaI intravenously. No effect.
2:18 p.m. Injected 232 mgm. NaI intravenously. No effect.
2:21 p.m. Injected 116 mgm. KCl intravenously. Immediate convulsions, dyspnea; animal died in spite of artificial respiration.

The results obtained on this limited number of animals with the massive doses of KI employed cannot be considered as evidence either for or against an accelerating effect of KI on growth. The fact that such large doses can be given over so long a time period (26–48 weeks), however, does indicate that growing rabbits develop a high tolerance to KI. The terminal doses in these experiments were larger than those reported by Sgalitzer (1908), Wadi (1928) and Shoemaker and Underhill (1932) as fatal when given as initial doses.

2. Effects of large amounts of KI given subcutaneously in adult rabbits. The great tolerance shown by young rabbits to increasing doses of KI suggested an experiment on the development of tolerance in adult animals (fig. 4). In these animals, KI in doses exceeding 1 gram I as KI per kgm. body weight caused a prompt loss of weight, severe diarrhea, and marked loss of appetite. The characteristic hind-limb paralysis was also observed and became more marked as the amount of KI was increased. That this weight loss, anorexia and paralysis are not due to the large amounts of potassium given is shown by the complete absence of these symptoms in the KCl-injected animals. At autopsy, none of these animals showed pleural effusion. Microscopically, definite fatty degeneration was observed in the livers of all animals injected with KI. Although these doses were markedly toxic, they are much larger than those reported as being rapidly fatal by the workers previously mentioned.

3. The comparative effect of large doses of NaI and KI. The greater toxicity of the potassium ion would suggest that NaI would be less toxic than KI when given subcutaneously in amounts equal in iodine content. This was investigated on one litter (fig. 5). Five animals received NaI (2.32 per cent), and four received KI (2.55 per cent). Both NaI and KI in the doses given caused profound depression of the animals, severe diarrhea, polyuria, and dyspnea for a variable time following the injection. One animal in each group died after a few days of severe diarrhea. The typical paralysis observed following KI was also observed following NaI. Although these doses caused marked symptoms of toxicity, growth occurred in both groups. KI did not appear to be more toxic than NaI as judged by the growth curves and the behavior of the animals.

4. Pathological changes. The most consistent and striking effect of prolonged iodine administration is shown by the thyroid gland. Macroscopically, this appears hard and avascular. Histologically, the thyroid shows marked flattening of the acinar epithelium and deposition of a large amount of hard, deeply staining colloid in the alveoli. The frequency of pleural effusions reported by Sgalitzer was not confirmed. Definite fatty degeneration was found in the livers of both adult and growing animals receiving large initial doses of iodide, but not in the livers of animals in the growth experiments who had developed a marked tolerance to the iodide. Massimo's finding (1930) of hemorrhagic infiltrations between the myocardial fibers and round cell infiltration beneath the endocardium after KI administration was observed in eight of the twenty hearts studied. Jastram's report (1920) that iodide caused an increased connective tissue formation in the ovaries could not be confirmed in the rabbit ovaries studied.

CONCLUSIONS

1. The oral or subcutaneous administration of KI to growing rabbits in progressively increasing doses up to 0.5 gram per kgm. body weight when given orally or 1.0 gram per kgm. body weight when given subcutaneously, does not alter appreciably the rate of growth.

2. Prolonged administration of KI leads to the development of a marked tolerance to the substance, so that doses which on first injection would be fatal can be given without producing toxic symptoms.

3. The acute effects following a large dose of the iodide ion are flaccidity and paralysis of the skeletal musculature, particularly of the hind limbs, and dyspnea.

4. The most striking histological change produced by prolonged iodide administration is a marked flattening of the epithelium of the thyroid acini and deposition of large amounts of colloid in the alveoli.

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